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10/566,157	01/27/2006	Shigeo Shibatani	10089/28	9830

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EXAMINER	
BAGGOT, BRENDAN O	
ART UNIT	**PAPER NUMBER**
1638	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/566,157	SHIBATANI ET AL.	
	Examiner	Art Unit	
	Brendan O. Baggot	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *20-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 January 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/06, 5/3/06, and 9/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Office acknowledges the receipt of Applicant's application filed on 1/27/06. Claims 1-21 are pending.

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-19, drawn to a method, a transformed plant and plant cell all for producing hyaluronic acid, classified in class 800, subclass 284.

II. Claims 20-21, drawn to an aminopolysaccharide – hyaluronic acid – s classified in class 536, subclass 53.

3. The inventions are independent or distinct, each from the other because:

4. Inventions I and II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case hyaluronic acid can be made by a materially different process, like bacterial fermentation or wet chemical synthesis.

5. Because these inventions are independent or distinct for the reasons given above and there would be a serious burden on the examiner if restriction is not required because the inventions have acquired a separate status in the art due to their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

7. During a telephone conversation with Applicant's representative on 10/27/06 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-19. Written affirmation of this election was made by applicant on 7 November 2006. Claims 20-21 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Sequence Listing

8. Applicant's computer readable format sequence listing has been entered.

Specification

9. Applicant is required to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification. The status of all citations of US filed applications in the specification should also be updated where appropriate.

10. The abstract of the disclosure is objected to because contains legalese: e.g. "comprises." Correction is required. *See* M.P.E.P. § 608.01(b).

Claim Rejections - 35 U.S.C. §112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 7 and 19 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

Claim 1 recites the limitation "a" DNA, "a" step of growing, "a" chlorella virus. There is insufficient antecedent basis for this limitation in the claim. Applicant is required to amend the claim to recite "the" DNA, "the" step of growing and "the" chlorella virus.

Information Disclosure Statement

12. An initialed and dated copy of Applicant's IDSs filed 4/27/06, 5/3/06, and 9/15/06, are attached to the instant Office Action.

Claim Rejections - 35 U.S.C. §101

35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 9-13, 15, 17, 19 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed inventions encompass untransformed plants and seeds, which are a product of nature and not one of the five classes of patentable subject matter. Claims 9-13, 15, 17, 19 are drawn to parts such as seeds and progeny of the transformed plant. Due to Mendelian

inheritance of genes, a single gene introduced into a parent plant would only be transferred at most to half the male gametes and half the female gametes. This translates into only three fourths of the progeny having at least a single copy of the transgene and one quarter of the progeny without a copy of the transgene. Since the claim encompasses progeny that lack the transgene, the claim encompasses plants and seeds that are indistinguishable from plants and seeds that would occur in nature. *See American Wood v. Fiber Disintegrating Co.*, 90 U.S. 566 (1874), *American Fruit Growers v. Brogdex Co.*, 283 U.S. 1 (1931), *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), *Diamond v. Chakrabarty*, 206 USPQ 193 (1980).

Claim Rejections - 35 USC § 112, 1st, paragraph, written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any polynucleotide of any length and sequence derived from any source encoding a hyaluronic acid synthase (HAS) from any source. Claims 1-19 are also broadly drawn to any polynucleotide which polynucleotide further

comprising a multitude of nucleotides of unspecified length or sequence encoding polypeptides with a multitude of deletions, substitutions, additions or insertions which polypeptide somehow synthesizes hyaluronic acid.

Applicants describe only membrane-associated hyaluronic acid synthases (E.C. 2.4.1.212) from *Chlorella* virus. (*See* specification page 26, line 16, page 26 line 3).

Applicants do not describe all hyaluronic acid synthases from every plant, bacterial, fungus, vertebrate and invertebrate or polynucleotides encoding them.

Claims 1-19 are also drawn to plant transformation with a polynucleotide containing unspecified and exemplified and non-exemplified deletions, substitutions, additions, and insertions in an amino acid sequence encoding a hyaluronic acid synthase. Thus claims 1-19 are broadly drawn to plant transformation with a multitude of unrelated sequences of undefined lengths encoding a multitude of proteins of unspecified length and sequence, with unspecified function.

In contrast, the specification only provides guidance for membrane-associated hyaluronic acid synthases (E.C. 2.4.1.212) from *Chlorella* virus. (*See* specification page 26, lines 16, 3, 17), the isolation of a known polynucleotide encoding hyaluronic acid synthase from *Chlorella*, and to tobacco transformation therewith. No guidance is provided regarding sequence domains which would be conserved throughout the broadly claimed genus of sequences, wherein said sequences domains are associated with hyaluronic acid synthase function.

Applicants fail to describe a representative number of hyaluronic acid synthases. Applicants only describe *Chlorella* hyaluronic acid synthase. Furthermore, Applicants

fail to describe structural features common to members of the claimed genus of hyaluronic acid synthases. Hence, Applicants fail to meet either prong of the two-prong test set forth by *Eli Lilly*. Furthermore, given the lack of description of the necessary elements essential for hyaluronic acid synthase, it remains unclear what features identify hyaluronic acid synthase. Since the genus of hyaluronic acid synthase has not been described by specific structural features such as conserved motifs, the active site, allosteric sites, or substrate binding domains, the specification fails to provide an adequate written description to support the breath of the claims.

The Federal Circuit has clarified the application of the written description requirement. The court stated that a written description of an invention "requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *See also Fiddes v. Baird*, 30 USPQ2d 1481 (Bd. Pat. App. & Int. 1993). The court also concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. Further, the court held that to adequately describe a claimed genus, Patent Owner must describe a representative number of the species of the claimed genus, and that one of skill in the art should be able to "visualize or recognize the identity of the members of the genus." Id.

Finally, the court held:

> A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Id.

See also MPEP Section 2163, page 174 of Chapter 2100 of the August 2005 version, column 1, bottom paragraph, where it is taught that

> [T]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

See also Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ 2d 1016 at 1021, (Fed. Cir. 1991) where it is taught that a gene is not reduced to practice until the inventor can define it by "its physical or chemical properties" (e.g. a DNA sequence).

Given the claim breadth and lack of guidance as discussed above, the specification fails to provide an adequate written description of the genus of sequences as broadly claimed. Given the lack of written description of the claimed genus of sequences, any method of using them, such as transforming plant cells and plants therewith, and the resultant products including the claimed transformed plant cells and plants containing the genus of sequences, would also be inadequately described. Accordingly, one skilled in the art would not have recognized Applicant to have been in possession of the claimed invention at the time of filing. *See* The Written Description Requirement guidelines published in Federal Register/ Vol. 66, No. 4/ Friday January 5, 2001/ Notices: pp. 1099-1111.

Claim Rejections - 35 U.S.C. §112, first paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *Chlorella* HAS gene, does not reasonably provide enablement for any HAS from any species or any sequence variants thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the claimed invention commensurate in scope with these claims.

The *Wands* court set forth the enablement balancing test:

> Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). *Wands* states at page 1404, "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the 'claims."

M.P.E.P. § 2164.01(a); *See also Ex Parte Forman* 230 USPQ 546, 547 (BdPatAppInt 1986); See also *Enzo Biochem, Inc., v. Calgene, Inc.*, 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999).

"35 U.S.C. §112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. . . In cases

involving. . .unpredictable factors. . .the scope of enablement. . .varies inversely with the degree of unpredictability. . ." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). It is well settled that "omission of minor details does not cause a specification to fail to meet the enablement requirement." *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1366, 42 USPQ2d 1001, 1005 (Fed. Cir. 1997).

The claims are broadly drawn to any polynucleotide of any length and sequence derived from any source encoding a hyaluronic acid synthase from any source. Claims 1-19 are also broadly drawn to any polynucleotide which polynucleotide further comprising a multitude of nucleotides of unspecified length or sequence encoding polypeptides with a multitude of deletions, substitutions, additions or insertions which polypeptide somehow synthesizes hyaluronic acid.

Applicants teach only membrane-associated hyaluronic acid synthases (E.C. 2.4.1.212) from *Chlorella* virus. (*See* specification page 26, line 16, page 26 line 3).

Applicants do not teach all hyaluronic acid synthases from every plant, bacteria, fungus, vertebrate and invertebrate or polynucleotides encoding them.

Claims 1-19 are also drawn to plant transformation with a polynucleotide containing unspecified and exemplified and non-exemplified deletions, substitutions, additions, and insertions in an amino acid sequence encoding a hyaluronic acid synthase. Thus claims 1-19 are broadly drawn to plant transformation with a multitude of unrelated sequences of undefined lengths encoding a multitude of proteins of unspecified length and sequence, with unspecified function.

In contrast, the specification only provides guidance for membrane-associated hyaluronic acid synthases (E.C. 2.4.1.212) from *Chlorella* virus. (*See* specification page 26, lines 16, 3, 17), the isolation of a known polynucleotide encoding hyaluronic acid synthase from *Chlorella*, and to tobacco transformation therewith. No guidance is provided regarding sequence domains which would be conserved throughout the broadly claimed genus of sequences, wherein said sequence domains are associated with hyaluronic acid synthase function.

The Nature of the Invention

The claims are drawn to methods and/or compositions relating to transgenic plants. The invention is in a class of inventions which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The Breadth Of The Claims

The claims are broadly drawn to and encompass all hyaluronic acid synthases from every plant, bacteria, fungus, vertebrate and invertebrate or polynucleotides encoding them.

Quantity Of Experimentation

The quantity of experimentation in this area is large since Applicant would have to identify homologs, clone the homologs, do enzyme kinetic experiments to confirm the enzymes have activity, select the homologs with high activity, transform a sufficient number of plants to offset position effects, select out the high copy number transformants, and screen the transformants for high expressing lines. This effort is an

inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The Unpredictability of the Art and the State of the Prior Art

There is abundant prior art to suggest that plant saccharide metabolism manipulation or upregulation is difficult, unpredictable and unsuccessful. A recent review by Bornke details a variety of problems seen in plant saccharide metabolism manipulation.

A recent paper by Bornke ((2002) Planta 214:356-364) details a variety of problems in plant saccharide pathway manipulation, including severe phenotypic alteration and misshapen flowers seen in plants expressing sucrose isomerase which suffered from carbon starvation. (*Id.*, abstract, page 363, left column; See specification, page 3, second paragraph). Thus, expressing any hyaluronic acid synthase in plants is unpredictable.

Applicant is also directed to Sweetlove et al, which teaches the transformation of whole plants for the accumulation of desired products via transformation with genes encoding enzymes involved in the synthesis of that product is unpredictable. Sweetlove et al found no difference in starch content, tuber number, tuber weight, or metabolite content between potatoes transformed with a gene encoding AGP and control plants, despite AGP enzyme activity four fold higher in transformed plants versus controls. (1996, Biochem. J. 320: 493-498, p. 495, entire page, and page 497, right column, paragraph 3).

Regarding the unpredictability of expressing heterologous proteins in plants, including bacterial proteins, Sutton taught that plant expression of bacterial proteins is unpredictable. Sutton sought to express the cry IIIA gene from *Bacillus thurigiensis var. tenebrionis* in transgenic tobacco. The crystal toxin genes (cry) from *B. thuringiensis* are difficult to express in plants even when under the control of efficient plant regulatory sequences. Sutton identified and eliminated five classes of sequences found throughout the cryIIIA gene that mimic eukaryotic processing signals and which may have been responsible for the low levels of transcription and translation. It was only after the creation of a 1974 bp synthetic gene that acceptable transgenic protein expression of the cryIIIA gene from *Bacillus thuringiensis var. tenebrionis* in transgenic tobacco could be achieved after undue trial and error experimentation. (1992) Transgenic research, Vol. 1, No. 5, pp. 228-36).

In fact, Broun et al, (1988, Science 282:1315-1317) teach that a change in only four amino acids will convert a Δ15 desaturase gene to a hydroxylase gene (see the abstract, at least). Thus, if sequences are identified only by hybridization to known sequences that encode hyaluronic acid synthase, one cannot conclude on this basis alone that these sequences also will encode a hyaluronic acid synthase having activity without additional evidence of the functionality or more knowledge of the particular structural features that are required for conferring this function.

Working Examples

The specification has no working examples of plant transformation with hyaluronic acid synthases other than with *Chlorella* HAS.

Guidance in the Specification

The specification, while suggesting the use of the *Chlorella* HAS, did not provide significant guidance on how to overcome art recognized problems in identifying which additions, insertions, deletions, or substations to the polynucleotide sequence could be tolerated, which plants have adequate substrate, which plants homeostatic mechanisms will not counterbalance any fluctuation in enzyme product, and which HAS DNA sequences are capable of efficient expression in every plant. Thus the skilled artisan is left with improperly extensive and undue trial and error experimentation.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

In the instant case, along with the absence of working examples, the relatively small amount of guidance in the specification, the unpredictability in the art and the large amount of experimentation would be necessary to achieve function balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Without sufficient guidance, determination of which insertions and etc. can be made without loss of function and without guidance on how to overcome the problems with making changes to a sequence without knowledge of the active site or crystal structure seen in HAS transgenic plants, it is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. *See In re Wands*, 858 F.2d 731,8 USPQ2nd 1400 Fed. Cir, 1988)

Therefore, given the breadth of the claims; the lack of guidance and working examples; the unpredictability in the art; and the state-of-the-art as discussed above, undue trial and error experimentation would be required to practice the claimed invention, and therefore the invention is not enabled throughout the broad scope of the claims.

Claim Rejections - 35 U.S.C. §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. §103(a).

The *Graham* court set forth the factual inquiries that are applied for determining obviousness under 35 U.S.C. 103(a):

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under

37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smeekens et al (6147280-US, Issued 14 November 2000) in view of DeAngelis, et al., (1997) Science 278:1800-1803 and further in light of Akasaka 4801539-US, issued 31 January 1989) and Mattes, et al., (5985668-US, Issued 16 November 1999).

Smeekens teaches a method of producing oligosaccharides comprising (1) a step of transforming a tobacco (col. 10, line 46) plant or plant cell using an expression recombinant vector (col. 9, line 60 to col. 10, line 40) comprising (i) a DNA encoding bacterial fructosyltransferase (column 9, line 20) or (ii) a DNA encoding a polypeptide, including one from or derived from a microorganism, having an amino acid sequence having one or more amino acid deletions, substitutions, additions or insertions (column 9, line 20, 45-55) in an amino acid sequence of the bacterial fructosyltransferase and having an activity of synthesizing oligosaccharides, (2) a step of growing (col. 10, line 48) a transformant obtained by transformation, and (3) a step of separating (Claim 1(f); col. 10, line 56) the oligosaccharides produced by the transformant. Smeekens also teaches angiosperms because Smeekens teaches tobacco (column 10, line 45).

Smeekens also teaches a method of making a transformed plant or plant cell (*Id.* @ column 10, line 39; col. 9, line 60 to col. 10, line 40; Claim 1) having an ability of producing oligosaccharides (Smeekens @ Figure 6A-6D; column 10, line 61)

comprising a step of transforming a plant cell using an expression recombinant vector, comprising (i) a DNA encoding bacterial fructosyltransferase (column 9, line 20), including wherein the fructosyltransferase is derived from a microorganism (column 9, line 20), or (ii) a DNA encoding a polypeptide, including wherein the fructosyltransferase is derived from a microorganism (column 9, line 20, 45-55), having an amino acid sequence having one or more amino acid deletions, substitutions, additions or insertions in an amino acid sequence of the fructosyltransferase (column 9, line 20, 45-55) and having an activity of synthesizing oligosaccharides. (col. 9, line 60 to col. 10, line 40). Smeekens also teaches tissue specific promoter. (Smeekens @ column 5, line 13).

Smeekens also teaches a transformed plant, plant cell, or progeny, tissue or organ thereof (col. 9, line 60 to col. 10, line 40; *Id.*, Claim 1), including one or two or more organs selected from a root, a stem, a rootstock, a leaf (column 10, line 54), a flower, a root truncation, a seed and a shoot apex, including an angiosperm (column 10, line 54), having an ability of producing oligosaccharides, obtained by transforming a plant cell using an expression recombinant vector comprising (i) a DNA encoding fructosyltransferase, including wherein the fructosyltransferase is derived from a microorganism, or (ii) a DNA encoding a polypeptide, including wherein the fructosyltransferase is the fructosyltransferase derived from a microorganism having an amino acid sequence having one or more amino acid deletions, substitutions, additions or insertions (column 9, line 20, 45-55) in an amino acid sequence of the

fructosyltransferase. (Smeekens @ col. 9, line 60 to col. 10, line 40, e.g.). Smeekens also teaches tissue specific promoter. (Smeekens @ column 5, line 13).

Smeekens does not teach a hyaluronic acid synthase able to make hyaluronic acid.

DeAngelis teaches hyaluronic acid synthase from Chlorella virus and Streptomyces pyogenes able to make hyaluronic acid (*See* figure 1, Accession No. U42580), synthesizing hyaluronic acid, and hyaluronic acid purification (*See* e.g., Figure 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the hyaluronic acid synthase of DeAngelis for the fructosyltransferase of Smeekens in a method of making transformed plants and plant cells to make transformed plants and plants cells for the purposes of producing hyaluronic acid in plants as taught and/or suggested by Smeekens in tobacco using the methods of Smeekens. One skilled in the art would have been motivated to generate the claimed invention because it is well known that reactor-based production using bacteria leads to the contamination by bacterial hemolytic toxins such as streptolysin as taught by Akasaka (column 1, lines 15-60) and that reactor-based production is not scalable and is more expensive than plant based production as taught or suggested by Mattes and by Smeekens. (Mattes, et al., @ column 1, line 20-26; Smeekens @ column 3, line 4). One would have been motivated to do so with a reasonable expectation of success because both fructosyltransferase and hyaluronic acid synthase are saccharide transferases, both produce alien sugars in plants, and the class of genes has already been expressed in plants as taught by Mattes for sucrose isomerase and as taught by

Smeekens for fructosyltransferase. Accordingly, one of ordinary skill in the art would have generated the claimed invention.

Remarks

17. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brendan O. Baggot whose telephone number is 571/272-5265. The examiner can normally be reached on Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg can be reached on 571/272-0975. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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